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A rare case of primary EBV infection causing acute acalculous cholecystitis



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ABSTRACT

Primary Epstein–Barr Virus (EBV) infection in children is common and frequently asymptomatic. While symptomatic patients typically present with features of infectious mononucleosis, a rare complication of primary EBV is acute acalculous cholecystitis. A 6 year old previously healthy boy presented with 6 days of low-grade fevers, non-bloody non-bilious vomiting, and periumbilical pain. Based on clinical, laboratory, and radiographic evidence, the patient was diagnosed with acute acalculous cholecystitis due to a primary EBV infection. The patient improved with supportive therapy and remained asymptomatic at follow-up. Overall, clinicians should consider EBV infection in the setting of multi-organ disease and blood dyscrasia. Furthermore, while the pathogenesis of EBV cholecystitis is still unclear, it is important to note that these patients may improve with supportive treatment and do not require surgical intervention.

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Epstein–Barr Virus (EBV) is a ubiquitous herpes virus that is generally spread among young children through salivary contact. Unlike adolescents, who typically develop features of infectious mononucleosis (IM) [1], primary EBV infections are frequently asymptomatic in children. When symptoms do occur, children present with a variety of manifestations including otitis media, diarrhea, abdominal complaints, upper respiratory infection, and infectious mononucleosis [2]. EBV can affect virtually any organ system, and a diverse range of diseases have been associated with the virus including pneumonia, pancreatitis, thrombocytopenia, myositis, glomerulonephritis and meningoencephalitis [3]. Here, we report a rare presentation of acute acalculous cholecystitis secondary to EBV infection in the pediatric population.

1. Case report

A 6 year old previously healthy boy presented to the ED with 6 days of low-grade fevers ($T_{\max} = 38^{\circ}\text{C}$), fatigue, and periumbilical pain. During this time, his pediatrician had obtained a rapid Strep throat swab which was negative. On the day of admission, his pain had increased in severity and migrated to the right lower quadrant.

He endorsed two episodes of non-bloody, non-bilious emesis, darker urine despite good fluid intake, and no changes in skin or stool.

In the ED, he was afebrile with normal vitals. Physical exam revealed tenderness to palpation in the right lower quadrant, palpable liver edge with a positive Murphy's sign, and a palpable spleen. His labs were remarkable for leukocytosis with a lymphocytic predominance (18,220 WBC/ μL , 80% lymphocytes), thrombocytopenia (73,000/ μL), elevated GGT (180 IU/L), transaminitis (AST 135, ALT 331), elevated alkaline phosphatase (569 IU/L), and hyperbilirubinemia (2.3 mg/dL, 1.5 mg/dL direct). Amylase, lipase, LDH, and uric acid were within normal limits, and blood and urine cultures were negative.

Right upper and lower quadrant ultrasounds were obtained and showed marked distention of the gallbladder with thickened hypervascular wall and mobile sludge, suggestive of acalculous cholecystitis (Fig. 1). Ultrasound of the appendix showed a hypervascular appendix with enlarged mesenteric lymph nodes (Fig. 2). In the ED, he was started on Unasyn (after receiving a single dose of Zosyn) and kept NPO on maintenance IV fluids. He was subsequently admitted to the Pediatric Surgery service for overnight observation and further management of appendicitis versus cholecystitis.

Given the multi-system involvement and blood dyscrasia, a systemic viral infection was suspected and Gastroenterology (GI)

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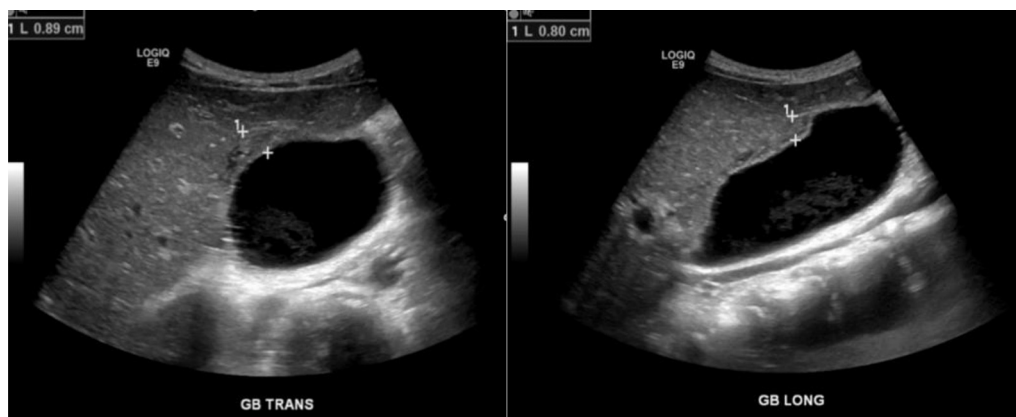


Fig. 1. Ultrasound of gallbladder showing thickened hypervascular wall.

and Hematology were consulted. An initial Monospot test was negative, but subsequent serologies revealed a positive EBV and CMV IgM and a positive EBV PCR. On hospital day 2, the patient remained afebrile and his abdominal pain had resolved. His transaminitis improved mildly (AST 113, ALT 249), and his thrombocytopenia and leukocytosis remained stable. He was continued on Unasyn in the setting of cholecystitis and continued to improve clinically with supportive therapy.

The patient was transferred to the General Medicine service and a repeat abdominal ultrasound with Doppler to evaluate the portal vasculature was ordered. An MRCP was also recommended to evaluate for distal filling defects. On hospital day 3, the abdominal ultrasound showed patent liver vessels with normal flow characteristics and decreased gallbladder distention. Given the decreased distention of the gallbladder and continued clinical improvement, the team, in consultation with GI and Surgery services, decided against obtaining the MRCP. The patient was discharged home the next day following complete resolution of his symptoms and toleration of an advanced diet, and he was scheduled for follow-up with both GI and Surgery, along with repeat labs in 1 week through his Pediatrician's office.

On follow-up, ALT was mildly elevated at 65 and all remaining labs were within normal limits. He continued to have hepatomegaly on exam and was found to have a new, diffuse maculopapular rash thought to be secondary to antibiotics. Unasyn was subsequently

discontinued. One month after discharge, he was asymptomatic with resolution of his hepatomegaly and a normal repeat ultrasound.

2. Discussion

Acute acalculous cholecystitis (ACC) accounts for about 10% of overall cholecystitis and is associated with a high mortality rate in the intensive care setting. The exact etiology of AAC remains unclear, but it is believed that conditions including severe trauma, burns, cardiovascular disease, major surgeries, and long term TPN lead to stasis, ischemia, and resultant inflammation of the gallbladder. In children however, AAC accounts for 30–50% of cholecystitis cases and is more commonly associated with congenital biliary anomalies; infectious diseases such as viral hepatitis, primary EBV and CMV infections, leptospirosis, Typhoid fever, Q-fever, Candida, and parasitic infections; and systemic disease such as Kawasaki disease [4].

We performed a review via PUBMED and found only 16 cases (not including the present case) of ACC secondary to EBV infection in the pediatric population, all of which were published between 2007 and 2014 (Table 1). Of these cases, 8 were reported in children and 8 in adolescents, and 15 of the 16 cases were reported in females. Thus, this is the second reported case of EBV associated ACC in the male pediatric population.

The clinical presentation of ACC in children is nonspecific. Among the 16 cases described above, the most common clinical symptoms were abdominal pain, fever, malaise, sore throat, and vomiting. Although pain and tenderness are often less localizable in younger children, our patient presented with periumbilical and right lower quadrant pain suggestive of appendicitis, which further complicated the diagnosis. His lower quadrant ultrasound showed a hypervascular appendix with enlarged mesenteric lymph nodes, suggestive of mesenteric lymphadenitis. It is important to note that although EBV has been reported to cause acute appendicitis [19], right lower quadrant pain associated with infectious mononucleosis is most commonly caused by transient mesenteric lymphadenitis and does not require laparoscopic intervention [20].

Common laboratory findings in primary EBV infection include lymphocytic predominant leukocytosis and abnormal liver function tests. However, patients developing acute acalculous cholecystitis have higher elevations in liver enzymes than patients with classical infectious mononucleosis (mean AST 515 vs 76.2 UI/L and ALT 552 vs 94.1 UI/L, bilirubin 5.5 vs 0.8 mg/dL) [14]. As with our patient, several of the reported patients with EBV associated ACC

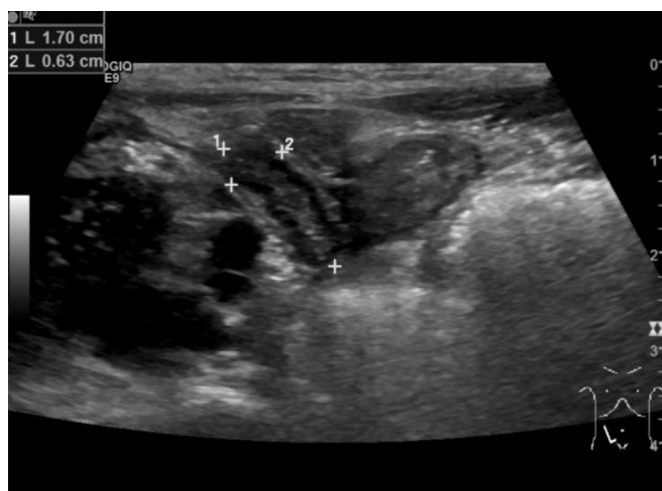


Fig. 2. Ultrasound finding of hypervascular appendix.

Table 1
Summary of previously reported cases of EBV-associated acalculous cholecystitis [5–18].

Author	Age	Sex	Clinical presentation	AST (UI/L)	ALT (UI/L)	Bilirubin (mg/dL)	Antibiotics
Prassouli et al. [5]	13	F	Fever, malaise, vomiting, abdominal pain	394	674	4	Yes
Lagona et al. [6]	4	F	Fever, anorexia, malaise, vomiting, abdominal pain	188	304	4.6	
Gora-Gebka et al. [7]	9	F	Fever, nausea, abdominal pain		179	4.6	Yes
Gora-Gebka et al. [7]	4	F	Fever, abdominal pain, acholic stools	388	423	2.9	Yes
Pelliccia et al. [8]	14	F	Fever, lymphadenopathy, pharyngitis, abdominal pain				
Iaria et al. [9]	18	F	Sore throat, anorexia, malaise, RUQ pain	220	328	7	Yes 48 h
Attilakos et al. [10]	5	M	Fever, sore throat, malaise	207	257	1.8	
Yang et al. [11]	20	F	Sore throat, malaise	171	299	0.7	Yes 24 h
Arya et al. [12]	16	F	Fever, malaise, vomiting, abdominal pain	479	211	8.5	Yes
Teke et al. [13]	8	F	Fever, vomiting, abdominal pain	569	496	4.6	No
Brunon et al. [14]	18	F	Fever, malaise	244	228	0.9	Yes
Brunon et al. [14]	20	F	Fever, malaise, pharyngitis, RUQ pain	453	494	2.2	Yes 48 h
Poddighe et al. [15]	7	F	No fever	3398	3324		Yes
Alkhoury et al. [16]	15	F	Fever, malaise, vomiting, abdominal pain	191	221	1.8	No
Suga et al. [17]	6	F	Fever, lymphadenopathy, abdominal pain	184	139	0.4	Yes
Kim et al. [18]	10	F	Fever, nausea, abdominal pain	311	489	1	Yes
Present case	6	M	Fever, malaise, vomiting, abdominal pain	135	331	2.3	Yes

AST, aspartate aminotransferase; ALT alanine aminotransferase; EBV, Epstein-Barr virus; F, female; h, hours M, male; RUQ, right upper quadrant.

presented with concurrent thrombocytopenia [7]. The pathogenesis is likely EBV-induced production of antibodies directed against platelets. Mild thrombocytopenia is a common complication following infection with EBV, and the finding of blood dyscrasia may support a viral etiology in cases where a diagnosis is unclear [21].

For diagnosis of ACC, ultrasound is the gold standard, with gallbladder wall thickness of 3.5 mm or greater and pericholecystic fluid being the two most reliable criteria [22]. In our case, ultrasound showed an edematous gallbladder with thickening up to 8 mm and mobile sludge within the gallbladder lumen. The patient's initial Monospot test was negative which reflects the high false negative rate reported during the first week of symptoms [23]. Subsequent EBV and CMV IgM antibodies were both positive, likely due to high levels of cross-reactivity [24]. EBV PCR finally confirmed the diagnosis of primary EBV infection.

Once acalculous cholecystitis is established, secondary infection with enteric pathogens is common [25]. Interestingly, among the 16 previously reported cases of EBV acute acalculous cholecystitis in the pediatric population, the majority discontinued antibiotics after the diagnosis of EBV primary infection. In our case, antibiotics were continued for 8 days due to concern for secondary infection, but were subsequently discontinued at follow-up after a maculopapular rash was seen on exam. Although there are currently no guidelines regarding the use of antibiotics in viral induced ACC, the favorable outcomes of the other reported cases suggest that continuing antibiotics may not be necessary in all cases.

The prognosis of ACC in the adult population is generally poor, with a mortality rate as high as 75% if treatment is delayed. For this reason, surgery is the mainstay treatment for adults [26]. In the pediatric population however, outcomes have been generally favorable and non-operative management appears safe for most patients.

3. Conclusion

Acute acalculous cholecystitis (ACC) is a rare complication of primary EBV infection in the pediatric population. Clinicians should consider EBV infection in the setting of multi-organ disease with abdominal pain and blood dyscrasia. Furthermore, most cases of EBV-associated ACC can be treated with medical management. Additional study is needed to identify the role of antibiotics following the diagnosis of ACC.

Conflicts of interest

The authors declare that there is no conflict of interests regarding the publication of this paper.

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